CEREMETRIX™

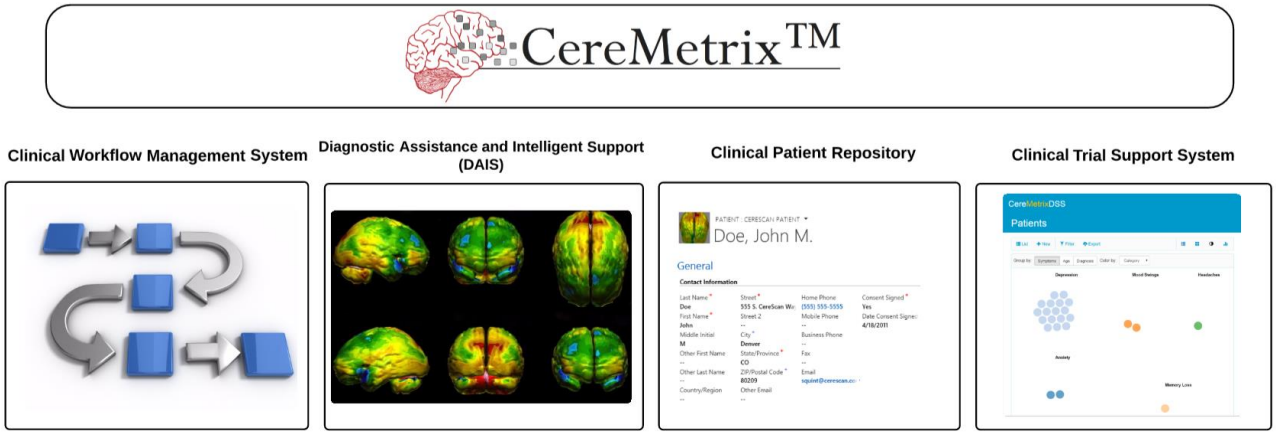
I. INTRODUCTION

CereScan, a company dedicated to providing the most accurate, comprehensive brain diagnoses available, continues to pursue disruptive changes in brain health standards of care by improving our already successful protocols and processes. CereMetrix™ is CereScan's patented database, which is a multifaceted entity that currently provides the architecture for our protocols and stores patient data for diagnosis and future analysis. As its utility expands, CereMetrix™ will eventually automate substantial components of image data analysis, assist reading and diagnosing physicians, provide intelligent information for treatment decisions, track patient outcomes, and contain searchable, accessible datasets for clinical trials and research (Figure 1). These functions, both established and in development, are expatiated in the following sections:

- Clinical Workflow Management System
- Diagnostic Assistance and Intelligent Support
- Clinical Patient Repository
- Clinical Trial Support System

This paper describes the current status of CereMetrix™ and the roadmap for future developments and applications. By implementing these strategies, CereScan will improve the quality of patient care and open opportunities for research initiatives across a broad spectrum of medical specialties.

Figure 1



II. CLINICAL WORKFLOW MANAGEMENT SYSTEM

OVERVIEW & FUNCTIONALITY

The primary clinical user interface of the CereMetrix™ system is the Clinical Workflow Management System. This module is used to track patients from initial inquiry, through the imaging process, to the preparation of the final diagnostic report. To ensure each patient receives a consistent and thorough diagnostic procedure that follows ACR (American College of Radiology) guidelines, the workflow verifies required checkpoints at each step in the process. There are currently nine steps, each with information that must be acquired before advancing to the next step: Gather Data, Qualify, Schedule, Intake Process, First-Scan Prep, Concentration Scan, Baseline Scan, Physician Reading, and Patient Review.

A critical module to be added in the future is the Diagnostic Assistance and Intelligent Support system, described below. All patient intake information, scan data, and assessments will be stored in a searchable, HIPAA-compliant, de-identified database with various search criteria such as symptomology, prior diagnoses, traumas, family history, and other data. The indexing of this data allows patterns or similarities to be found between the current patient and previous ones within the database. Upon the implementation of this module, the referring physician will have access to a matching patient registry along with their diagnoses, treatment options and outcomes. This registry will aid the physician in determining the most appropriate treatment plan for the patient. Once established, CereMetrix™ will track the treatments and outcomes of the patient for future reference with new patients.

APPLICATIONS & BENEFITS

The Clinical Workflow Management System value is primarily useful in the clinical setting. This process ensures that a reliable product is delivered for each patient and that the data obtained is consistent across patients. While the concept of workflow management as it relates to other imaging facilities is valuable, this process is specifically tailored to the CereScan process of brain imaging. The main benefit of this CereMetrix™ module is that the consistency and precision of the clinical process is enforced through the workflow, ensuring a positive patient experience and accurate outcomes.

III. DIAGNOSTIC ASSISTANCE & INTELLIGENT SUPPORT

OVERVIEW

The Diagnostic Assistance and Intelligent Support (DAIS) system will improve multiple aspects of the CereScan workflow. DAIS is primarily designed to assist the physician during the diagnostic process and will provide results derived from the combination of quantitative SPECT data and the clinical information from the patient's Intake Package. The vision of DAIS is to increase the reading speed and accuracy of physicians while strengthening their confidence in their diagnoses. As a tool created to analyze current and historic patient data, all information will be stored and accessible within CereMetrix™ for future use.

PROTOCOL

SPECT IMAGE PROCESSING

Processing SPECT brain scans is the first task of DAIS. CereScan will continue to utilize third-party normative databases for comparison and processing of each new patient brain scan. Each SPECT patient dataset generates a 64 x 64 x 64 matrix of voxels with each voxel containing counts of gamma rays. These counts are direct measures of cerebral blood flow, i.e., the more counts, the more blood flow. Voxels can be grouped into regions of interest (ROIs), such as anatomical structures, function-specific areas and sub-regions in the brain. Once processed, the blood flow in each voxel within the patient data is mathematically measured against each corresponding voxel in the normative database. The result classifies each voxel as having "normal" or "abnormal" perfusion levels. To visualize differences in blood flow, a color map is generated from this voxel data and applied to the images.

Abnormal voxels do not typically occur in isolation. Usually, clusters of abnormal voxels are observed throughout the brain as a result of injury or disorder. Morphological image processing will allow these clusters to be located and measured to determine their impact on the physiological function of each ROI.

The result of these calculations will allow for the pre-population of CereScan's unique brain activity worksheet, a document that concisely describes and quantifies the location and severity of abnormal blood flow within each ROI. The reading physician will view this document alongside the processed images to determine an impression.

Frequently, the scanning protocol requires two scans: a concentration (or activation) scan and a baseline scan. A two-scan protocol is prescribed when a disorder that disrupts blood supply in the frontal lobe is suspected. By presenting the patient with a stimulating task prior to scanning, frontal lobe perfusion levels are analyzed to confirm or eliminate such disorders from diagnoses. The activation scan is compared to the baseline scan to determine how stimulation of the frontal lobe with a cognitive task affects perfusion levels. An identical brain activity worksheet is generated for the concentration scan and displayed concurrent with the baseline activity worksheet.

Years of research have associated brain ROIs with human function and subsequent symptoms. As such, a classification system will be integrated to store these known functions and symptoms with each voxel cluster in a particular region. For example, voxels within the occipital lobe, the area responsible for vision, will be associated with symptoms like vision defects, hallucinations, and reading problems. This information will be imperative for creating the Symptom-Matching Report described below.

PHYSICIAN "BLIND" READ

CereScan's reading physicians initially interpret each brain scan without any biasing clinical information or other data about the patient. The pre-populated brain activity worksheet will allow the physician to simultaneously interpret the processed images and analyze mathematically-derived data. The physician will be able to add comments directly to the worksheet based on experience, analysis and visual interpretation of the images. When utilized, commenting the activity worksheet will document the physician's thought process for future reference. After synthesizing the objective, quantitative results, the physician will record his or her initial impressions.

DATA CONSULTATION & VALIDATION

DAIS will then provide the physician with three reports. The first report includes the patient's Intake Package and the results of the neuropsychiatric and/or cognitive assessments. A comments section at the end of this report will be available for the physician to make notes.

Secondly, the Symptom-Matching Report will identify the symptoms related to the locations of abnormal voxels. In this report, "Software-Reported" symptoms are then compared to any "Patient-Reported" symptoms recorded during intake. Results of the comparisons are classified as "Matched," "Software Unmatched," or "Patient Unmatched." To reduce ambiguity, the symptoms programmed within the software and those reported by the patient are chosen from a list of standardized keywords.

The third document is the Pattern-Matching Report. Abnormal voxel location and distribution data is iteratively compared to an age-appropriate normative dataset within CereMetrix™. Images in the dataset that match the incoming patient's data will be aggregated and reported along with their associated blood flow patterns.

INDICATIONS & FINDINGS

After reviewing these reports, the physician views a window with his or her initial impressions, comments from the previous reports, and the suggested diagnosis as determined by DAIS. Once the physician has synthesized all available information, he or she uses standardized language to prepare the final Indications and Findings Report.

APPLICATIONS & BENEFITS

CERESCAN & AFFILIATE CLINICS

The physician's read is the most time consuming and subjective component of the current CereScan process; one read may take up to an hour to complete. By implementing DAIS, the most tangible benefits will be improved speed, accuracy and consistency of the reading process. The reading physician will no longer manually enter data based on visual interpretation of a blood flow color scale. Instead, all reports will be automatically generated from quantitative SPECT data and information within the Intake Package. The physician will be able to focus on the significance of the data rather than the tedious recording of colored images. Although the DAIS algorithms generate these calculations and reports, the physician is ultimately responsible for the final diagnosis. The gain in speed, accuracy and consistency provided by DAIS will reduce the need to linearly add reading physicians as CereScan expands its geographic footprint.

DAIS will also enhance the training protocol for new CereScan reading physicians. It will eliminate subjectivity while providing helpful reports for determining a diagnosis. Both the Symptom and Pattern-Matching Reports supplement the perfusion data, but in different ways. Symptoms associated to damage in each area of the brain are integrated into the Symptom-Matching Report while the Pattern-Matching Report pulls images and diagnoses, made by experienced reading physicians, from historic patient data stored within CereMetrix™. These reports act as checkpoints to validate the training physician's initial impressions.

Finally, DAIS has potential applications for many other imaging fields. Medical imaging, in any modality, requires physician interpretation. Implementing clinical decision support systems into any medical

imaging workflow will improve the speed, accuracy, consistency, and validity with which images are read. Thus, our DAIS system may be morphed into one that can be used for any number of modalities.

SOFTWARE AS A SERVICE

The capabilities and deliverables of DAIS will make it an exceptionally valuable module within our licensable Software as a Service (SAAS) commercial offering. Organizations, both large and small, will utilize DAIS in a variety of ways. Hospitals, for example, may use it to assist their physicians during the diagnostic process. While the current CereScan imaging protocols are significantly more robust and comprehensive than that used in the hospital environment, DAIS will allow our protocols to be easily implemented in that setting. Researchers, in contrast, may be more attracted to the searchable, extensive, data output of DAIS. Finally, as part of the Clinical Trial Support System described below, pharmaceutical companies, medical device companies, and Contract Research Organizations can license this module to support their investigation of drugs and devices for brain interventions. Since each of those entities must conduct clinical trials to obtain FDA approvals, DAIS can easily be introduced to monitor and track brain function over the duration of the trials. With our customizable SAAS, any of these groups will be able to license DAIS individually or in a package to best satisfy their needs.

IV. CLINICAL PATIENT REPOSITORY

OVERVIEW

The clinical patient repository module of CereMetrix™ is the backbone of the system and necessary for the other modules to work. This database is configured to be a one-to-many relationship between the patient data and the multiple visits to a CereScan facility for imaging and other diagnostic purposes. When utilized with multiple Scan Encounters, this data structure will allow tracking of quantitative changes in brain function over time. This ability will prove particularly valuable when investigating the impacts of interventions on brain function and patient quality of life. Additionally, protocols and algorithms will be established in order to provide a system to measure the progression or amelioration of certain brain disorders.

ORGANIZATION OF PATIENT INFORMATION

INFORMATION AND HISTORY

This data is collected during an extensive intake process designed to uncover any possible brain-affecting events or behaviors. Through medical records and patient interviews, CereScan clinicians attempt to gather all possible medical details that could cause or contribute to the patient's condition.

SCAN ENCOUNTER

The Scan Encounter summarizes the patient's most relevant and current information at the time of their scan. A patient may have multiple Scan Encounters if they are scanned multiple times, but a two-scan protocol (concentration and baseline scans, 48 hours apart) is considered only one Scan Encounter. Any information that changes between scan visits will be captured in this data structure.

IMAGE DATA

After being processed through DAIS, the voxel-level image data from each scan is stored within the "Scan Interpretations" portion of each Scan Encounter. These data are critical components of the patient's electronic health record and of CereScan's ever-expanding brain diagnostic warehouse. Storing this data makes it valuable for comparisons with future scans and for use in the Clinical Trial Support System described below.

DIAGNOSTIC FINDINGS

After the brain activity worksheet is generated and the image data is read, a detailed findings report is compiled. This information is then written into the "Scan Details" section of the Scan Encounter within the database.

TREATMENTS

In the future, we will track patients' treatments and outcomes. Collecting this data will enable the creation of the Decision Support System previously discussed (Section II) while contributing valuable information to the Clinical Trial Support System (Section V).

APPLICATIONS & BENEFITS

The primary purpose of the Clinical Patient Repository is to catalog pertinent clinical patient information and imaging data in order to build a comprehensive brain evaluation system; it is critical to the functionality of the Decision Support System and DAIS. The results of this searchable, HIPAA-compliant database will provide better diagnostic and research tools to the medical community. CereMetrix™ is one of a kind and will offer unique opportunities to advance the understanding of brain dysfunctions and thus improve patient outcomes. CereMetrix™ currently has over 3400 patients and is ever-growing. The larger the database of image and patient clinical data, the better the diagnostic intelligence contained in the data.

STRUCTURED AND SEARCHABLE DATABASE

The searchable data warehouse consists of structured, de-identified clinical and image data indexed in a way that permits "Google" type searches against any of the attributes (age, diagnosis, symptoms, etc.). The interface displays the results and allows filtering into groupings of "bubbles", each representing a single patient. Any bubble may be selected to reveal more information about that specific patient. Furthermore, the sorted bubbles may be color-coded to reflect additional sort criteria when identifying cohorts.

ELECTRONIC HEALTH RECORD

At its core, CereMetrix™ is a sophisticated electronic health records (EHR) system with advanced diagnostic and analytical capabilities. An integral part of every EHR system is its ability to exchange patient's health records with other EHR systems. CereMetrix™ has been built with capabilities to exchange basic patient demographic and clinical information via securely encrypted HL7 web service interfaces. CereMetrix™ utilizes a secure Microsoft SQL Server database platform housed in a HIPAA-compliant data

center that is protected by a secure Cisco firewall. This infrastructure allows CereScan to perform the most basic requirements of any clinical facility – store and protect patient information.

V. CLINICAL TRIAL SUPPORT SYSTEM

OVERVIEW

The Clinical Trial Support System is a critical module that will be available for researchers via the SAAS offering. This module may be customized and implemented independently as an analytical and informatics tool for either clinical or research applications. The analytical piece will enable users to perform patient-to-patient and patient-to-normal assessments in order to monitor disease progression or to compare pre- and post-intervention perfusion levels. This module will be designed to meet the requirements of *Informatics for Integrating Biology and the Bedside* (i2b2; developed by NIH) to aid cohort identification, hypothesis generation, and retrospective data analysis.

FUNCTIONALITY

ANALYTICAL

As an analytical tool, the primary purpose of the Clinical Trial Support System is to enable patient study over time. Though the standard CereScan protocol analyzes the baseline scan against a normative database at each voxel (Section III), these workflows will provide the ability to compare current patient data against their previously obtained scans with the same granularity. This will allow for precise observation of disease and injury progression as well as the effects of pharmaceuticals, therapies, and/or devices on brain perfusion levels.

The protocol for these investigations will be customizable, increasing the number of options available to the researcher or physician. The comparative database may be changed from a set of normal scans to a set comprised of scans from a single disease, disorder, or injury type or from ROIs within the brain. Any non-normal dataset can be automatically compiled from our extensive library of patient histories, images, and diagnoses. For example, some users may specify which brain areas are evaluated; other users may wish to study the global impacts of a nonspecific drug therapy; others may want to isolate ROIs surrounding an implanted electrode. Once developed, DAIS will possess these capabilities and will provide the researcher with menus to automatically construct their own comparative datasets.

INFORMATICS

The Clinical Trial Support System will aid archival researchers in multiple ways. A dynamic search interface will allow users to select filters that can segregate patients with certain characteristics within CereMetrix™. These filters might include age, gender, symptoms, incoming diagnoses, treatments, military history, substance or alcohol abuse, and many more. This will allow for potential study subjects to be identified, for hypotheses to be investigated, and for correlations and data patterns to be discovered and analyzed. After users have selected subsets of the database through this process, they will be able to export data for further analysis.

APPLICATIONS & BENEFITS

The Clinical Trial Support System will be most appealing to pharmaceutical companies, medical device manufacturers, and Contract Research Organizations conducting randomized clinical trials required for FDA approval of new drugs and medical devices. The CereMetrix™ database, protocols, and analytical tools will be able to facilitate research conducted in pursuit of solutions for neurological and psychiatric disorders. As evidenced above, the value of CereMetrix™ lies not only in its existing image and patient library, but also in its ability to create custom, non-normal databases and tracking algorithms for specific trials along with specified normative databases of control groups that are integral to clinical trials.

The clinical trial market for treating brain-related dysfunctions has immense potential to grow due to the enormous attention given to conditions such as TBI, Alzheimer's, Parkinson's and other disorders. Veterans groups, NIH programs, and the federal government's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative are examples of the focus being placed on brain research today. As the federal government continues to fund research dedicated to understanding, treating, and interacting with the brain, the results of those efforts will eventually face the FDA for implementation in humans. Our Clinical Trial Support System will provide researchers, drug and device companies, and CROs the platform needed to prove the safety, efficacy, and security of their discoveries.

VI. CONCLUSIONS/OUTLOOK FOR FUTURE

CereMetrix™ is a multifaceted intelligent diagnostic system that continually gets smarter with each patient added to the database. Better diagnoses will lead to better treatments, better patient outcomes, and lower healthcare costs. Future versions will refine the brain diagnostic process while exploring its adaptation for other imaging modalities. This system is geographically independent and can be utilized anytime, anywhere in a low-cost, tele-medicine model available to all practitioners. The system's ability to extract quantitative data from brain scans and correlate that data with symptoms and outcomes will change the way medical imaging is used. This unique approach will open the door to a revolutionary diagnostic breakthrough in healthcare.